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APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A  
FILING DATE.

APPLICATION NUMBER: 60/519,302

FILING DATE: *November 12, 2003*

RELATED PCT APPLICATION NUMBER: PCT/US04/37793

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## PROVISIONAL APPLICATION COVER SHEET

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Docket Number	235.0054 0160		Type a plus sign (+) inside this box >	+  111203
INVENTOR(s)/APPLICANT(s)				
Name (last, first, middle initial)		RESIDENCE (CITY, AND EITHER STATE OR FOREIGN COUNTRY)		
Ferguson, Duncan C.		Bogart, Georgia		
TITLE OF THE INVENTION (280 characters max)				
DNA SEQUENCE AND EXPRESSED RECOMBINANT GLYCOPROTEINS RELATED TO FELINE THYROTROPIN (TSH)				
CORRESPONDENCE ADDRESS				
Mueting, Raasch & Gebhardt, P.A. P.O. Box 581415 Minneapolis				
Attn: Victoria A. Sandberg				
STATE	Minnesota	ZIP CODE	55458-1415	COUNTRY
United States of America				
ENCLOSED APPLICATION PARTS (check all that apply)				
<input checked="" type="checkbox"/>	Specification	Number of Pages	10	Small Entity Statement
<input type="checkbox"/>	Drawing(s)	Number of Sheets	_____	Other (specify) _____
METHOD OF PAYMENT (check one)				
<input checked="" type="checkbox"/>	A check or money order is enclosed to cover the Provisional filing fees		PROVISIONAL FILING FEE AMOUNT	(\$) 160.00
<input checked="" type="checkbox"/>	The Commissioner is hereby authorized to charge any additional required fees or credit overpayment to Deposit Account Number: <u>13-4895</u>			

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government:

No.

Yes, the name of the U.S. Government agency and the Government contract number are: \_\_\_\_\_

Respectfully submitted,

SIGNATURE Victoria A. Sandberg

TYPED OR PRINTED NAME Victoria A. Sandberg

Date Nov 12, 2003

REGISTRATION NO. 41,287

Additional inventors are being named on separately numbered sheets attached hereto.

**PROVISIONAL APPLICATION FILING ONLY**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Duncan C. Ferguson

Docket No.: 235.0054 0160

Title: DNA SEQUENCE AND EXPRESSED RECOMBINANT GLYCOPROTEINS RELATED TO FELINE THYROTROPIN (TSH)

Assistant Commissioner for Patents  
MAIL STOP: PROVISIONAL APPLICATION  
P.O. Box 1450  
Alexandria, VA 22313-1450

We are transmitting the following documents along with this Transmittal Sheet (which is submitted in triplicate):

PROVISIONAL PATENT APPLICATION including:

Specification (10 consecutively numbered pgs, including 0 claims);  
 Drawings (\_\_\_\_ figures on \_\_\_\_ sheets);  
 Photographs (\_\_\_\_ sheets);  
 Provisional Application Cover Sheet (1 pg).  
 A check in the amount of \$ 160.00 to pay the provisional application filing fee.  
 Verified statement(s) establishing small entity status of this application under 37 C.F.R. 1.9 and 1.27 is/are enclosed.  
 An itemized return postcard.  
 An Assignment of the invention to \_\_\_\_\_ and Recordation Form Cover Sheet (\_\_\_\_ pgs).  
 A check in the amount of \$40.00 to cover the Assignment Recording Fee.  
 Computer readable form of "Sequence Listing." Applicants state that the paper copy form of the "Sequence Listing" section of the present application, and the computer readable form submitted herewith, are the same.  
 Other: \_\_\_\_\_.

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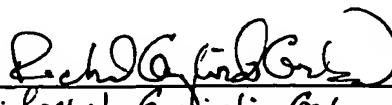
By:   
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Facsimile: 612/305-1228

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Date of Deposit: November 12, 2003

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By:   
Name: Rachel C. Englehardt

(PROVISIONAL TRANSMITTAL UNDER RULE 1.10)

**DNA SEQUENCE AND EXPRESSED RECOMBINANT GLYCOPROTEINS RELATED TO  
FELINE THYROTROPIN (TSH)**

**A United States Provisional Patent Application**

## DNA SEQUENCE AND EXPRESSED RECOMBINANT GLYCOPROTEINS RELATED TO FELINE THYROTROPIN (TSH)

### ABSTRACT

Newly established sequence and DNA constructs of the alpha and beta subunits of the pituitary glycoprotein thyrotropin (TSH) of the cat, and a new process to express the glycoproteins in high quantity. Constructs include sequence for individually expressing the alpha subunit (including signal sequence and FLAG affinity tag with a Factor Xa cleavage site. The beta subunit DNA also includes intron 1 to enhance expression in mammalian cells. Another recombinant engineered "yoked" peptide engineered is a single-chain DNA sequence which encodes the alpha subunit and the beta subunit (including the first intron) linked by the C-terminal peptide of human chorionic gonadotropin. When expressed in mammalian cells (human embryonic kidney cells), this "yoked" glycoprotein is bioactive

### TECHNOLOGY DESCRIPTION

Our laboratory is the first to discover the cDNA sequence of pituitary feline alpha subunit. A report of tiger alpha subunit cDNA is 97.8% similar but not identical. Projected amino acid sequence of the 24 amino acid signal sequence and 96 amino acid alpha subunit differs from that of the tiger by 3 amino acids (97.5% homology). In addition, our feline alpha construct includes 98 additional upstream bases which we amplified from feline pituitary RNA.

We believe that the enhanced *in vivo* expression levels of the construct not only make it unique to the cat, but also an improved expression construct.

The report of the beta subunit genomic DNA structure including expressed sequence as well as the first intron has not been previously reported. The use of the cDNA for human chorionic gonadotropin (HCG) C-terminal peptide (xxamino acids) to link the alpha and beta subunits has been a strategy used previously in other laboratories and also in our laboratory for canine TSH. However, the application to the new sequence of feline TSH is novel. Please see attached sequence information for available recombinant constructs.

We are currently evaluating monoclonal antibodies developed against ovine and canine TSH for crossreactivity to feline TSH. Our next phase of research will confirm whether these monoclonal antibody pairs can detect feline TSH in a sensitive "sandwich" assay. If sensitivity is inadequate, we are preparing a monoclonal antibody later this month against the feline alpha subunit which will be paired with our 14H9.E4 beta subunit specific monoclonal antibody which we have already shown will detect heterodimeric and yoked feline TSH. We believe that the final demonstration of the fact that these recombinant standards can be used for immunoassay standards will strengthen their commercial value. We have preliminary evidence with crude proteins supporting this value but will soon do additional studies of it. Demonstration of in vitro (cell culture and adenylate cyclase stimulation) and in vivo bioactivity (increase in serum thyroid hormone concentrations and increased radioiodide uptake in cats) will serve as proof of bioactivity of the expressed constructs.

**Vectors and cells – pEAK10™ expression vector and pEAK™ cells (modified HEK cells) from Edge Biosystems, 19208 Orbit Drive, Gaithersburg, MD 20879-4149**

No transfer agreement – this vector was used to transfect the mammalian pEAK cells (modified Human Embryonic Kidney (HEK) cells for transient expression of alpha and beta subunits of feline TSH (TSH alpha/beta), the expression of feline alpha subunit alone, and the yoked feline TSH construct. Using puromycin selection, the line fTSHalpha /pEAK line and yfTSH/pEAK cell lines were created in our laboratory

## APPLICATIONS OF THE TECHNOLOGY

1. Expression of recombinant feline thyrotropin and its subunits as immunoassay standards and immunogens for improved immunoassays against feline TSH. Such assays, particularly if sensitive enough to detect TSH suppression, would be a valuable diagnostic tool for the diagnosis of feline hyperthyroidism. A less sensitive assay would still be able to allow veterinary practitioners to monitor success of treatment with antithyroid drugs.
2. Recombinant heterodimeric or yoked feline TSH as a species-specific bioactive stimulus of thyroid function. Used as a thyroid radiosensitizing agent to increase the efficacy of a radioiodide ablative dose in thyroid adenomas and particularly in nonfunctional carcinomas. Because the structure is identical in thyrotropin, follicle stimulating hormone (FSH) and luteinizing hormone (LH), the alpha subunit can be used also to develop the subunit for combination with different beta subunits of those pituitary glycoproteins
3. Development of permanent cell lines to express feline alpha subunit – already accomplished – cell line fTSHalpha /pEAK line – the commercial value resides in the ability to independently produce the feline pituitary alpha subunit common to feline FSH, LH and TSH.
4. Development of permanent cell lines which express the yoked feline TSH construct – already accomplished – cell line yfTSH/pEAK line – the commercial value resides in the ability to produce a bioactive and immunoreactive glycosylated single-chain feline TSH.

## REFERENCES

1. Genbank AF354939. *Panthera tigris a...*[gi:13561973] Baldwin,D.M., Bedows,E., Miller-Lindholm,A.K., Sherman,G.B. and Wilken,J.A. Characterization of recombinant tiger gonadotropins; Unpublished
2. Genbank AF354939. *Panthera tigris a...*[gi:13561973] Baldwin,D.M., Miller-Lindholm,A.K., Wilken,J.A., Sherman,G.B. and Bedows,E.; unpublished; Submitted (20-FEB-2001) Eppley Institute/Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, 986805 Nebraska Medical Center, Omaha, NE 68198-6805, USA
3. Genbank, AF408393. *Panthera tigris a...*[gi:22535904], Liao,M.J., Zhu,M.Y. and Zhang,A.J. *Panthera tigris altaica* pituitary glycoprotein hormone alpha subunit. Unpublished; Submitted (08-AUG-2001) College of Life Sciences, Zhejiang University, Wenshan Road 232, Hangzhou, Zhejiang 310012, China
4. Genbank AF354939. *Panthera tigris a...*[gi:13561973] Crichton,E.G., Bedows,E., Miller-Lindholm,A.K., Baldwin,D.M., Armstrong,D.L., Graham,L.H., Ford,J.J., Gjorret,J.O., Hyttel,P., Pope,C.E., Vajta,G. and Loskutoff,N.M. Efficacy of Porcine Gonadotropins for Repeated Stimulation of Ovarian Activity for Oocyte Retrieval and In Vitro Embryo Production and Cryopreservation in Siberian Tigers (*Panthera tigris altaica*) *Biol. Reprod.* 68 (1), 105-113 (2003)

## SEQUENCE INFORMATION

### A. Construct of Feline Thyrotropin-beta Subunit with First Intron

1 30  
 5'(GAA TTC)ATG ACT GCT ATC TAC CTG ATG TCC GTG CTT  
     met thr ala ile tyr leu met ser val leu  
 31 75  
 TTT GGC CTG GCA TGT GGA CAA GCG ATG TCT TTT TGT TTT CCA ACT  
     phe gly leu ala cys gly gln ala met ser phe cys phe pro thr  
 76 120  
 GAG TAT ATG ATG CAT GTC GAA AGG AAA GAG TGT GCT TAT TGC CTA  
     glu cys met met his val glu arg lys glu cys ala tyr cys leu  
 121 162  
 ACC ATC AAC ACC ACC ATC TGT GCT GGA TAT TGT ATG ACA CGG  
     thr ile asn thr thr ile cys ala gly tyr cys met thr arg  
*Intron 1*  
 163 *GTATGTAGITCATCTCACTCTTTAGCTGAAAATTAGATAAACCTAGACT*  
*CAGTCCATTCTATCCAGAAAGGAAATGAGATAAATCACACCTCATTCACAGACCTAACGGT*  
*CATTGGCTCCTAGAGGTAGAGTCCCTAGGTTATAATATACGGACCTACTCCATACAGTTGGTA*  
*CAGATAATTTCACAATAGTTTACTCCCAAAGTTTATTAAACCTTATCTTGTCCCACGGATCA*  
*AGGATAAAAGAGAGGTGTGTGTATGTCATTTTTGTCTATAGGATTCAAGTGTGGATA*  
*TGCTGAATTGGTATTGGGAATGGGACTAAGGAATCCTCCCCAGTCCATTGTATCTATGGG*  
*ATGTAAGCGAATTAACATTTGCTCCTCTGTGCTTCCCTCAG* 580  
 581 625  
 GAT ATC AAT GGC AAA CTG TTT CTT CCC AAA TAT GCT CTG TCC CAA  
     asp ile asn gly lys leu phe leu pro lys tyr ala leu ser gln  
 626 670  
 GAT GTT TGC ACC TAC AGA GAC TTC CTG TAC AAG ACT GTA GAA ATA  
     asp val cys thr tyr arg asp phe leu tyr lys thr val glu ile  
 671 715  
 CCA GGA TGC CCA CAC CAT GTT ACT CCC TAT TTC TCC TAC CCG GTA  
     pro gly cys pro his his val thr pro tyr phe ser tyr pro val  
 716 760  
 GCT GTA AGC TGT AAA TGT GGC AAG TGT AAT ACT GAC TAT AGC GAC  
     ala val ser cys lys cys gly lys cys asn thr asp tyr ser asp  
 761 805  
 TGC ATA CAT GAG GCC ATC AAG ACA AAT GAT TGT ACC AAA CCC CAG  
     cys ile his glu ala ile lys thr asn asp cys thr lys pro gln  
 806 835  
 AAG TCC GAT GTG GTA GGA GTT TCT ATC TAA (GCGGCCGC<sub>(4)</sub>(AT)<sub>5</sub>3'  
     lys ser asp val val gly val ser ile stop

### Key

( ) denotes the Eco RI restriction sites

**Bold** denotes signal sequence

**Bold/italic** denotes the intron 1 sequence

B. Feline Alpha Subunit Construct

(GAATTC) GCCCTT

1

45

**AGT TAC TGA GAA ATC ACA AGA CGA AGC CAA AAT CCC TCT TCA GAT**

ser tyr OPA glu ile thr arg arg ser gln asn pro ser ser asp

46

90

**CCA CGG TCA ACT GCC CTG ATC ACA TCC TGC AAA AAG TCC GGA GGA**

pro arg ser thr ala leu ile thr ser cys lys lys ser gly gly

91

135

**AGG AGA GCC ATG GAT TAC TAC AGA AAA TAT GCA GCT GTC ATT CTG**

arg arg ala met asp tyr tyr arg lys tyr ala ala val ile leu

136

180

**GCC ATA CTC TCT GTG TTT CTG CAT ATT CTC CAT TCT TTT CCT GAT**

ala ile leu ser val phe leu his ile leu his ser phe pro asp

181

225

**GGA GAG TTT ACA ATG CAG GGG TGC CCA GAA TGC AAG CTA AAG GAA**

gly glu phe thr met gln gly cys pro glu cys lys leu lys glu

226

270

**AAC AAA TAC TTC TCC AAG TTG GGT GCC CCA ATT TAT CAA TGC ATG**

Asn lys tyr phe ser lys leu gly ala pro ile tyr gln cys met

271

315

**GGC TGC TGC TTC TCC AGA GCA TAC CCC ACT CCA GCA AGG TCC AAG**

gly cys cys phe ser arg ala tyr pro thr pro ala arg ser lys

316

360

**AAG ACA ATG TTG GTC CCA AAG AAC ATC ACC TCA GAA GCC ACA TGC**

lys thr met leu val pro lys asn ile thr ser glu ala thr cys

361

405

**TGT GTG GCC AAA GCC TTT ACC AAG GCC ACG GTA ATG GGA AAT GCC**

cys val ala lys ala phe thr lys ala thr val met gly asn ala

Continued on next page

406

450

AAA GTG GAG AAT CAC ACA GAG TGC CAC TGC AGC ACT TGC TAT CAC

lys val glu asn his thr glu cys his cys ser thr cys tyr his

451 459

492

**CAC AAG ATT (ATC GAA GGT GCT<sub>(1)</sub>)(GAC TAC AAG GAC GAT GAC GAT**

his lys ile ile glu gly ala asp tyr lys asp asp asp asp

493 495 510

AAG<sub>(2)</sub>) (TAA<sub>(3)</sub>) (GCGGCCGC<sub>(4)</sub>)(TATG)<sub>5</sub> 3'

lys

**Bold** denotes 24 amino acid unexpressed signal sequence as per structure in other species

***Bold italics*** denotes sequence upstream from expressed but not secreted signal sequence; only reported in equine; whether it is expressed is not clear.

( ) denotes Eco R1 restriction site from TOPO Blunt vector

Underlined denotes additional sequence from TOPO Blunt vector

( <sub>1</sub> ) denotes Factor XA site

( <sub>2</sub> ) denotes Flag tag

( <sub>3</sub> ) denotes stop codon

( <sub>4</sub> ) denotes Not1 restriction enzyme site

( )<sub>5</sub> denotes extra bases needed for restriction enzyme to work

C. Yoked Feline TSH

1 30  
5'(GAA TTC)ATG ACT GCT ATC TAC CTG ATG TCC GTG CTT  
met thr ala ile tyr leu met ser val leu

31 75  
TTT GGC CTG GCA TGT GGA CAA GCG ATG TCT TTT TGT TTT CCA ACT  
phe gly leu ala cys gly gln ala met ser phe cys phe pro thr  
76 120  
GAG TAT ATG ATG CAT GTC GAA AGG AAA GAG TGT GCT TAT TGC CTA  
glu cys met met his val glu arg lys glu cys ala tyr cys leu  
121 162  
ACC ATC AAC ACC ACC ATC TGT GCT GGA TAT TGT ATG ACA CGG  
thr ile asn thr thr ile cys ala gly tyr cys met thr arg

*Intron 1*

163 *GTATGTAGTTCATCTCACCTCTTTAGCTGAAAATTAGATAAACCTAGACT*  
*CAGTCCATTCTATCCAGAAAGGAAATGAGATAAAATCACAAACCTCATTACAGACCT*  
*AACGGTCATTGGCTCTTAGAGGTAGAGTCCCTAGGTTATAATATACGGACCTACTCC*  
*ATACAGTTGGTACAGATAATTCTACAATAGTTTACTCCAAAGTTATTTAACCTT*  
*ATCTTGTCTCCACGATCAAGGATAAAAGAGAGGGTGTGTGTATGTCTTTTTGT*  
*CTCTATAGGATTCAAGTGTGGATATGCTGAATTGGTATTGGGAATGGACTAAGGAAT*  
*CCTCCCCAGTCTATTGTATCTATGGGATGTAAGCGAATTAACATTGCTTCCCTCT*  
*TCTGTGCTTCCCTCAG 580*

581 625  
GAT ATC AAT GGC AAA CTG TTT CTT CCC AAA TAT GCT CTG TCC CAA  
asp ile asn gly lys leu phe leu pro lys tyr ala leu ser gln

626 670  
GAT GTT TGC ACC TAC AGA GAC TTC CTG TAC AAG ACT GTA GAA ATA  
asp val cys thr tyr arg asp phe leu tyr lys thr val glu ile

671 715  
CCA GGA TGC CCA CAC CAT GTT ACT CCC TAT TTC TCC TAC CCG GTA  
pro gly cys pro his his val thr pro tyr phe ser tyr pro val

716 760  
GCT GTA AGC TGT AAA TGT GGC AAG TGT AAT ACT GAC TAT AGC GAC  
ala val ser cys lys cys gly lys cys asn thr asp tyr ser asp

761 805  
TGC ATA CAT GAG GCC ATC AAG ACA AAT GAT TGT ACC AAA CCC CAG  
cys ile his glu ala ile lys thr asn asp cys thr lys pro gln

806 *beta specific primer sequence\** 850  
AAG TCC GAT GTG GTA GGA GTT TCT ATC *CTP linker* CAG GAC TCC TCA AAG GCC  
lys ser asp val val gly val ser ile gln asp ser ser lys ala

851 892  
*CTP linker (continued)*  
CCT TCC GCC AGC CTT CCA AGC CCA ACG CGT CTC CCG GGG CCC  
pro ser ala ser leu pro ser pro thr arg leu pro gly pro

\*reverse complement in construct *Afl III ligation site*

893 CTP linker (continued)

alpha  
specific primer sequence 931 \*

TCG GAC ACC CCG ATC CTC CCA CAA | TTT CCT GAT GGA GAC

ser asp thr pro ile ile pro gln phe pro asp gly glu

932

971

TTT ACA ATG CAG GGG TGC CCA GAA TGC AAG CTA AAG GAA

phe thr met gln gly cys pro glu cys lys leu lys glu

972

1016

AAC AAA TAC TTC TCC AAG TTG GGT GCC CCA ATT TAT CAA TGC ATG

Asn lys tyr phe ser lys leu gly ala pro ile tyr gln cys met

1017

1061

GGC TGC TGC TTC TCC AGA GCA TAC CCC ACT CCA GCA AGG TCC AAG

gly cys cys phe ser arg ala tyr pro thr pro ala arg ser lys

1062

1106

AAG ACA ATG TTG GTC CCA AAG AAC ATC ACC TCA GAA GCC ACA TGC

lys thr met leu val pro lys asn ile thr ser glu ala thr cys

1107

1151

TGT GTG GCC AAA GCC TTT ACC AAG GCC ACG GTA ATG GGA AAT GCC

cys val ala lys ala phe thr lys ala thr val met gly asn ala

1152

1196

AAA GTG GAG AAT CAC ACA GAG TGC CAC TGC AGC ACT TGC TAT CAC

lys val glu asn his thr glu cys his cys ser thr cys tyr his

1197

1205

CAC AAG ATT (ATC GAA GGT GCT<sub>(1)</sub>)(GAC TAC AAG GAC GAT GAC GAT

his lys ile ile glu gly ala asp tyr lys asp asp asp asp

1239 1241

1256

AAG<sub>(2)</sub> (TAA<sub>(3)</sub>) (GCGGCCGC<sub>(4)</sub>)(TATG)<sub>5</sub> 3'

lys

\*as written

Key

( ) denotes the Eco RI restriction sites

**Bold** denotes signal sequence

***Bold italics*** denotes intron 1 sequence 1=Factor XA site

( *1*) denotes Factor XA site

( *2*) denotes Flag tag

( *3*) denotes stop codon

( *4*) denotes Not1 restriction enzyme site

( *5*) denotes extra bases needed for restriction enzyme to work

The present invention is illustrated by the preceding examples. It is to be understood that the particular examples, materials, amounts, and procedures are to be interpreted broadly in accordance with the scope and spirit of the invention as set forth herein. The foregoing description and examples have been given for clarity of understanding only. No unnecessary limitations are to be understood therefrom. The invention is not limited to the exact details shown and described, for variations obvious to one skilled in the art will be included within the invention described herein.

The complete disclosure of all patents, patent applications, and publications, and electronically available material (including, for example, nucleotide sequence submissions in, e.g., GenBank and RefSeq, and amino acid sequence submissions in, e.g., SwissProt, PIR, PRF, PDB, and translations from annotated coding regions in GenBank and RefSeq) cited herein are incorporated by reference.

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